REMARKS

Claim 33 has been canceled herein, as have withdrawn claims 1 to 30 and 34 to 36. New claims 37 to 42 have been added. Thus, claims 31, 32, and 37 to 42 are pending and presently under examination.

Regarding the amendments and new claims

Claim 31 has been amended to indicate that a sample from an individual to be diagnosed is contacted with pbrA having greater than 70% amino acid identity with SEQ ID NO: 2 or SEQ ID NO: 3. The amendment is supported throughout the specification, for example, at page 25, lines 19-27, which indicates that the term pbrA can describe a polypeptide having greater than 50%, 60%, 70% or greater amino acid sequence identity with SEQ ID NO: 2 or SEQ ID NO: 3.

Claim 31 additionally has been amended to indicate that pbrA is purified, partially purified or present in a whole or fractionated *Pseudomonas* cellular extract. The amendment to claim 31 is supported throughout the specification, for example, at page 37, lines 3-5, which indicates that a *Pseudomonas* antigen useful in the invention can be purified, partially purified or present in a whole or fractionated *Pseudomonas* cellular extract, and at page 5, lines 2-7, which indicates that a *Pseudomonas* antigen can be a *P. fluorescens* antigen such as pbrA.

New claim 37 is directed to a diagnostic method of the invention in which a sample from an individual to be diagnosed is contacted with purified pbrA or an immunoreactive fragment thereof. The new claim is supported throughout the specification, for example, at page 37, lines 3-17, which indicates that a *Pseudomonas* antigen useful in the invention can be purified or partially purified, and at page 24, lines 17-23, which indicates that the pbrA-v antigen (SEQ ID NO: 2) was isolated from patient UCLA #268.

New claim 38 is directed to a diagnostic method of the invention in which the recited pbrA has greater amino acid sequence similarity to SEQ ID NO: 2 or SEQ ID NO: 3 than to the *P. aeruginosa* protein pvds (SEQ ID NO: 7). New claim 38 is supported throughout the specification, for example, at page 25, lines 17-19, which discloses that a pbrA polypeptide can exhibit greater similarity to SEQ ID NO: 2 or SEQ ID NO: 3 than to the *P. aeruginosa* protein pvds (SEQ ID NO: 7).

New claim 39 is directed to a diagnostic method of the invention in which the recited pbrA has the amino acid sequence of SEQ ID NO: 2 or an immunoreactive fragment thereof, and new claim 40 is directed to a diagnostic method of the invention in which the recited pbrA has the amino acid sequence of SEQ ID NO: 2. New claim 41 is directed to a diagnostic method of the invention in which the recited pbrA has the amino acid sequence of SEQ ID NO: 3 or an immunoreactive fragment thereof, and new claim 42 is directed to a diagnostic method of the invention in which the recited pbrA has the amino acid sequence of SEQ ID NO: 3. These new claims are supported, for example, by original claim 33 and throughout the specification, for example, at page 6, lines 14-27, which indicates that the diagnostic methods of the invention can be practiced, for example, with pbrA having the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3 or with an immunoreactive fragment of one of these sequences.

Regarding the rejection of claims 31 to 33 under 35 U.S.C. § 112, first paragraph

The rejection of claims 31 to 33 under the first paragraph of 35 U.S.C. § 112 as allegedly lacking enablement is respectfully traversed. The Office Action asserts that the specification lacks enablement for pbrA antigens or immunoreactive fragments other than full-length SEQ ID NO: 2 (pbrA-v) or SEQ ID NO: 3 *(P. fluorescens* pbrA*)*. In support of this position, the Examiner cites Salgaller et al. as allegedly showing that single amino acid changes in an immunodominant MAGE-1 peptide reduce lysis by cytotoxic T lymphocytes, and further cites Fox (U.S. Patent No. 4,879,213) as allegedly showing that short linear peptides may fail to mimic the secondary or tertiary structure of antigenic determinants. Based on these references, the Examiner alleges that it would have been unpredictable which modified pbrA sequences or pbrA fragments would have been useful in diagnosing Crohn's disease.

Applicants contend that, in view of the guidance in the specification, one skilled in the art would have been able to practice the full scope of the invention without undue experimentation. In particular, the specification provides guidance regarding the use of a variety of pbrA polypeptides and immunoreactive fragments other than full-length SEQ ID NO: 2 (pbrA-v) or SEQ ID NO: 3 *(P. fluorescens* pbrA*)*. In this regard, the specification teaches that a pbrA polypeptide can be, for example, a naturally occurring pbrA polypeptide having substantial amino acid sequence similarity to SEQ ID NO: 2 or SEQ ID NO: 3 (page 25, lines 6-11). The specification provides further guidance by teaching that a pbrA polypeptide useful in the invention also can be, for example, an isotype variant or homolog of SEQ ID NO: 2 or

SEQ ID NO: 3, such as a *Pseudomonas* homolog of SEQ ID NO: 2 or SEQ ID NO: 3 (page 25, lines 11-17). As additional guidance to the skilled person, the specification teaches that a naturally occurring pbrA polypeptide is an iron regulatory sigma factor and that a pbrA may exhibit greater sequence similarity to SEQ ID NO: 2 or SEQ ID NO: 3 than to the sequence of homologous sigma factors from microbial organisms outside the *Pseudomonas* family, for example, greater sequence similarity to SEQ ID NO: 2 or SEQ ID NO: 3 than to the *P. aeruginosa* protein pvdS (page 24, line 29, to page 25, line 1; and page 25, lines 11-19). Thus, in view of the guidance in the specification, only routine work, and not undue experimentation, would have been required for the skilled person to practice the claimed diagnostic methods with various pbrA polypeptides in addition to SEQ ID NO: 2 (pbrA-v) and SEQ ID NO: 3 (*P. fluorescens* pbrA).

The specification further teaches that immunoreactive fragments of pbrA can be useful in the invention. Such an immunoreactive fragment is a peptide or polypeptide portion of pbrA that has immunoreactivity as defined by the ability of an anti-pbrA antibody-positive sample such as pbrA-reactive Crohn's disease patient sera to form a complex with the fragment (page 43, lines 23-30; page 45, lines 1-12). As set forth in the specification, routine assays such as ELISA assays can be particularly useful for assaying immunoreactivity of a fragment of pbrA (page 45, lines 9-12). The specification further teaches that one skilled in the art can assay, if desired, a panel of peptides spanning the entire sequence of a pbrA polypeptide such as SEQ ID NO: 2 or SEQ ID NO: 3 in order to corroborate immunoreactivity of pbrA fragments (page 50, lines 10-31). Thus, in view of the guidance in the specification, only routine laboratory work would have been required to make and confirm the immunoreactivity of portions of a pbrA polypeptide such as portions of SEQ ID NO: 2 or SEQ ID NO: 3.

Applicants further respectfully submit that the claimed invention is enabled irregardless of the references cited in the Office Action. Firstly, the Salgaller et al. reference, which allegedly reports that single amino acid changes in an immunodominant MAGE-1 peptide reduce lysis by cytotoxic T lymphocytes, is not relevant to the claimed invention. Specifically, the cited reference by Salgaller et al. relates to recognition of T lymphocytes rather than antibody reactivity and, thus, has no bearing on the claimed invention. Secondly, the cited reference by Fox (U.S. Patent No. 4,879,213) is alleged to show that short linear peptides <u>may</u> not reproduce the secondary or tertiary structure of antigenic determinants. However, Applicants respectfully point out that there is no requirement that an immunoreactive fragment of pbrA be a "short linear

peptide." In particular, while the secondary or tertiary structure of a few antigenic determinants may not be reproduced by short linear peptides, one skilled in the art readily would have been able to prepare a relatively long pbrA fragment that retains secondary or tertiary structure. Furthermore, only routine work would have been required to confirm immunoreactivity of pbrA fragments including short linear peptides using, for example, pbrA-reactive patient sera, for example, sera that immunoreact with full-length SEQ ID NO: 2 or SEQ ID NO: 3 using well-known ELISA assays as discussed above. For these reasons, the two references cited in the Office Action do not demonstrate that the claimed diagnostic methods lack enablement.

In view of the above remarks, Applicants respectfully request that the Examiner reconsider and remove the enablement rejection of claims 31 to 33 under the first paragraph of 35 U.S.C. § 112.

Regarding the rejection of claims 31 to 33 under 35 U.S.C. § 112, second paragraph

The rejection of claims 31 to 33 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite for reciting the terms "pbrA" and "immunoreactive fragment" is respectfully traversed.

Regarding the term "pbrA"

Applicants submit that the term "pbrA" is clear to the skilled person in view of the specification. As set forth in the subject application, a pbrA polypeptide has substantially the same amino acid sequence as a pbrA having amino acid sequence SEQ ID NO: 2 or SEQ ID NO: 3 (page 24, lines 17-23), and, thus, pbrA is defined by a structural relationship with the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3 (page 24, lines 17-21). Such a pbrA polypeptide having substantially the same amino acid sequence as SEQ ID NO: 2 or SEQ ID NO: 3 can be, for example, an isotype variant or homolog of SEQ ID NO: 2 or SEQ ID NO: 3 such as a *Pseudomonas* homolog of SEQ ID NO: 2 or SEQ ID NO: 3 (page 25, lines 11-17). The specification further teaches that, in nature, pbrA is an iron regulatory sigma factor and that a pbrA polypeptide can be a polypeptide which exhibits greater sequence similarity to SEQ ID NO: 2 or SEQ ID NO: 3 than to homologous sigma factors from microbial organisms outside the *Pseudomonas* family (page 25, lines 11-17). In view of the above remarks, Applicants maintain that the term "pbrA" is clear to the skilled person in view of the specification.

Nevertheless, in order to further prosecution of the subject application, claim 31 has been amended to more clearly indicate that a pbrA polypeptide is defined by a structural relationship with the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3. Specifically, independent claim 31 has been amended to indicate that the claimed methods are practiced with pbrA having greater than 70% amino acid sequence identity with SEQ ID NO: 2 or SEQ ID NO: 3. In view of the above remarks and amendments, Applicants respectfully request that the Examiner reconsider and remove this ground for rejecting claims 31 to 33 as allegedly indefinite.

Regarding "immunoreactive fragments" of pbrA

Applicants further respectfully assert that the term "immunoreactive fragment" is clear and definite to the skilled person in view of the specification. In particular, the specification teaches that an immunoreactive fragment of pbrA is a peptide or polypeptide portion of pbrA that has immunoreactivity as defined by the ability of an anti-pbrA antibody-positive sample to form a complex with the fragment. Useful anti-pbrA antibody-positive samples include, for example, pbrA-reactive Crohn's disease patient sera, which can be used to assess immunoreactivity using a routine immunoassay such as an ELISA (page 43, lines 23-30; page 45, lines 1-12). Thus, in view of the common meaning of the term "immunoreactivity" and what is set forth in the specification, it is clear that an immunoreactive fragment is a polypeptide portion of a pbrA polypeptide such as SEQ ID NO: 2 or SEQ ID NO: 3 that forms a complex with an anti-pbrA antibody-positive sample such as pbrA-reactive Crohn's disease patient sera. Accordingly, Applicants respectfully request that the Examiner reconsider and remove this ground for rejecting claims 31 to 33.

Having addressed each ground for rejection of the claims under the second paragraph of 35 U.S.C. § 112, Applicants submit that claims 31 to 33 are clear and definite to the skilled person in view of the specification. Applicants therefore request that the Examiner reconsider and remove the rejection of claims 31 to 33 under 35 U.S.C. § 112, second paragraph.

Regarding the rejection of claims 31 to 33 under 35 U.S.C. § 102(b)

The rejection of claims 31 to 33 under 35 U.S.C. §102(b) as allegedly anticipated by Targan et al., U.S. Patent No. 5,932,429, is respectfully traversed. Although Targan et al. do not describe the molecule pbrA, it is alleged that the ANCA, pANCA, SAPPA and anti-*Saccharomyces cerevisiae* antibody (ASCA) markers described in Targan et al. meet the broad definition of "pbrA" given that these markers share the function of being able to diagnose Crohn's disease. For this reason, the Examiner concludes that Targan et al., U.S. Patent No. 5,932,429, anticipates the claimed invention.

Applicants submit that the cited patent by Targan et al. cannot anticipate the claimed invention, which involves contacting a sample from an individual to be diagnosed with pbrA or an immunoreactive fragment thereof and detecting a complex containing pbrA or an immunoreactive fragment of pbrA. In contrast to the claimed invention, Targan et al. report diagnostic methods which rely on determining the presence of ANCA, pANCA, SAPPA or ASCA rather than a pbrA. As acknowledged in the Office Action, Targan et al. do not disclose the molecule pbrA. Furthermore, in view of the definition of pbrA set forth in the specification and further in view of the claim language, Applicants submit that the recited pbrA antigen clearly does not encompass the structurally unrelated ANCA, pANCA, SAPPA and ASCA markers utilized by Targan et al.

In particular, the specification teaches that a pbrA polypeptide has substantially the same amino acid sequence as SEQ ID NO: 2 or SEQ ID NO: 3 (page 24, lines 17-23). A pbrA polypeptide therefore is not defined by the functional ability to diagnose Crohn's disease as implied by the Examiner but rather by a structural relationship with the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3. Furthermore, in order to more clearly indicate the structural characteristics of pbrA, independent claim 31 has been amended to indicate that the claimed methods are practiced with pbrA having greater than 70% amino acid sequence identity with SEQ ID NO: 2 or SEQ ID NO: 3. Thus, it is clear that the recited pbrA has significant structural similarity to SEQ ID NO: 2 or SEQ ID NO: 3 and is not defined merely by diagnostic function. In view of the fact that the Examiner has acknowledged that Targan et al. do not disclose the molecule pbrA, Applicants maintain that the claimed invention is novel over Targan et al.

Accordingly, Applicants respectfully request that the Examiner reconsider and remove the rejection of claims 31 to 33 under 35 U.S.C. §102(b) as allegedly anticipated by Targan et al.

CONCLUSION

In view of the above remarks, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned agent.

Respectfully submitted,

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